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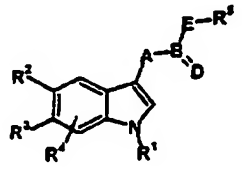
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: NEW HYDROXYINDOLES, THEIR USE AS PHOSPHODIESTERASE 4 INHIBITORS AND METHOD FOR PRODUCING SAME

(54) Bezeichnung: NEUE HYDROXYINDOLE, DEREN VERWENDUNG ALS INHIBITOREN DER PHOSPHODIESTERASE 4 UND VERFAHREN ZU DEREN HERSTELLUNG



(1)

(57) Abstract

The invention relates to hydroxyindoles of formula (1), where R^1 and R^5 are $-C_{1..12}$-alkyl, $-C_{2..12}$-alkenyl, mono-, bi- or tricyclic carbocycles, mono-, bi- or tricyclic heterocycles, carbo- or heterocyclic spirocycles, and R^2 and R^3 can be hydrogen or -OH, whereby at least one of the two substituents must be -OH. The invention also relates to their use as phosphodiesterase 4 inhibitors and to a method for producing them.

(57) Zusammenfassung

Hydroxyindole der Formel (1), worin R^1, R^5 für $-C_{1..12}$-Alkyl, $-C_{2..12}$-Alkenyl, -mono-, bi- oder tricyclische Carbocyclen; -mono-, bi- oder tricyclische Heterocyclen, -carbo- oder heterocyclische Spirocyclen steht; R^2, R^3 können Wasserstoff oder -OH sein, wobei mindestens einer von beiden Substituenten -OH sein muß; deren Verwendung als Inhibitoren der Phosphodiesterase 4 und Verfahren zu deren Herstellung.

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New hydroxyindoles, their use as phosphodiesterase 4 inhibitors and method for producing same

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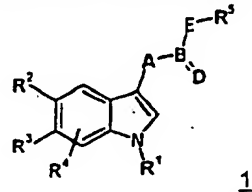
(56) Related Art
AU 40158/97
EP 490263
DILLARD ET AL, J.MED.CHEM, 1996, 39, 5119-5136

New Hydroxyindoles, Their Use as Inhibitors of Phosphodiesterase 4 and Processes for Their Preparation

Technical field

The invention relates to substituted hydroxyindoles of the general formula 1



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processes for their preparation, pharmaceutical preparations which contain these compounds, and the pharmaceutical use of these compounds, which are inhibitors of phosphodiesterase 4, as active compounds for the treatment of disorders which can be affected by inhibition of phosphodiesterase 4 activity in immunocompetent cells (eg. macrophages and lymphocytes) by the compounds according to the invention.

Prior art

The activation of cell membrane receptors by transmitters leads to the activation of the "second messenger" system. Adenylate cyclase synthesises active cyclic AMP (cAMP) or cyclic GMP (cGMP) from AMP and GMP. These lead, for example, to relaxation in smooth muscle cells or to inhibition of mediator release or synthesis in inflammatory cells. The breakdown of the "second messenger" cAMP and cGMP is carried out by the phosphodiesterases (PDE). To date, 7 families of PDE enzymes (PDE1-7) are known, which differ by their substrate specificity (cAMP, cGMP or both) and the dependence on other substrates (eg. calmodulin). These isoenzymes have different functions in the body and are prominent to different extents in the individual cell types (Beave JA, Conti M and Heaslip RJ, Multiple cyclic nucleotide phosphodiesterases, Mol. Pharmacol. 1994, 46: 399-405; Hall IP, Isoenzyme selective phosphodiesterase inhibitors; potential clinical uses, Br. J. clin. Pharmacol. 1993, 35: 1-7). As a result of inhibition of the various PDE isoenzyme types, there is an accumulation of cAMP or cGMP in the cells, which can be therapeutically utilised (Torphy TJ, Livi GP, Christensen SB, Novel Phosphodiesterase Inhibitors for the Therapy of Asthma, Drug News and Perspectives 1993, 6: 203-214).

In the cells important for allergic inflammation (lymphocytes, mast cells, eosinophilic granulocytes, macrophages), the prevailing PDE isoenzyme is of type 4 (Torphy, J T. and Undem, B. J., Phosphodiesterase inhibitors: new opportunities for the treatment of asthma, Thorax 1991, 46: 512-523). The inhibition of PDE 4 by suitable inhibitors is therefore considered as an important starting point for the therapy of a large number of allergically induced disorders (Schudt Ch, Dent G, Rabe K, Phosphodiesterase Inhibitors, Academic Press London 1996).

An important property of phosphodiesterase 4 inhibitors is the inhibition of the release of tumour necrosis factor α (TNFα) from inflammatory cells. TNFα is an important pro-

inflammatory cytokine, which affects a large number of biological processes. TNFα is released, for example, from activated macrophages, activated T lymphocytes, mast cells, basophils, fibroblasts, endothelial cells and astrocytes in the brain. It has a self-activating effect on neutrophils, eosinophils, fibroblasts and endothelial cells, as a result of which various tissue-destroying mediators are released. In monocytes, macrophages and T lymphocytes, TNFα brings about the increased production of further pro-inflammatory cytokines such as GM-CSF (granulocyte-macrophage colony-stimulating factor) or interleukin-8. On account of its inflammation-promoting and catabolic action, TNFα plays a central part in a large number of disorders, such as inflammation of the airways, inflammation of the joints, endotoxic shock, tissue rejection, AIDS and numerous other immunological disorders. Inhibitors of phosphodiesterase 4 are thus also suitable for the therapy of disorders of this type which are associated with TNFα.

Chronic obstructive pulmonary diseases (COPD) are widespread in the population and also have great economic importance. Thus COPD diseases cause about 10-15% of all illness costs in the developed countries and about 25% of all cases of death in the USA are to be attributed to this cause (Norman P.: COPD: New developments and therapeutic opportunities, Drug News Perspect. 11 (7), 431-437, 1998), however the patients at the time of death are usually over 55 years old (Nolte D.: Chronische Bronchitis-eine Volkskrankheit multifaktorieller Genese. Atemw.-Lungenkrkh. [Chronic bronchitis-a widespread disease of multifactorial origin]. 20 (5), 260-267, 1994). The WHO estimates that COPD will be the third most frequent cause of death within the next 20 years.

The syndrome of chronic obstructive lung diseases (COPD) summarises various syndromes of chronic bronchitis with the symptoms coughing and expectoration and progressive and irreversible impairment of lung function (exhalation is particularly affected). The course of the disease is episodic and often complicated by bacterial infections (Rennard S.I.: COPD: Overview of definitions, Epidemiology, and factors influencing its development. Chest, 113 (4) Suppl., 235S-241S, 1998). In the course of the disease, the lung function continuously decreases, the lungs become increasingly emphysematous and the respiratory distress of the patients is obvious. This disease clearly adversely affects the quality of life of the patients (dyspnoea, low exercise tolerance) and significantly reduces their life expectancy. The main risk factor besides environmental factors is smoking (Kummer F.: Asthma und COPD. Atemw.-Lungenkrkh. 20 (5), 299-302, 1994; Rennard S.I.: COPD: Overview of definitions, Epidemiology, and factors influencing its development. Chest, 113 (4) Suppl., 235S-241S, 1998) and therefore men are clearly more often affected than women. As a result of the change in living habits and the increase in the number of smokers, this picture, however, will change in future.

The current therapy aims only at the alleviation of the symptoms, without causally intervening in the progression of the disease. The use of long-acting Beta2 agonists (eg. salmeterol) possibly in combination with muscarinergic antagonists (eg. ipratropium) improves the lung function by bronchodilatation and is employed routinely (Norman P.:

COPD: New developments and therapeutic opportunities, Drugs News Perspect. 11 (7), 431-437, 1998). A large part in the COPD episodes is played by bacterial infections, which have to be treated with antibiotics (Wilson R.: The role of infection in COPD, Chest, 113 (4) Suppl., 242S-248S, 1998; Grossman R.F.: The value of antibiotics and the outcomes of antibiotic therapy in exacerbations of COPD. Chest, 113 (4) Suppl., 249S-255S, 1998). As yet, the therapy of this disease is unsatisfactory, particularly with respect to the continuous decrease in lung function. New therapeutic approaches which affect inflammatory mediators, proteases or adhesion molecules could be very promising (Barnes P.J.: Chronic obstructive disease: new opportunities for drug development, TiPS 10 (19), 415-423, 1998).

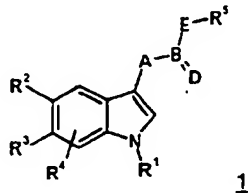
Independently of the bacterial infections complicating the disease, a chronic inflammation which is dominated by neutrophilic granulocytes is found in the bronchi. The mediators and enzymes released by neutrophilic granulocytes, *inter alia*, have been held responsible for the structural changes observed in the airways (emphysema). The inhibition of the activity of the neutrophilic granulocytes is thus a rational approach to prevent or to slow down progression of COPD (impairment of lung function parameters). An important stimulus for the activation of the granulocytes is the pro-inflammatory cytokine TNFα (tumour necrosis factor). Thus it is known that TNFα stimulates the formation of oxygen radicals by neutrophilic granulocytes (Jersmann, H.P.A.; Rathjen, D.A. and Ferrante A.: Enhancement of LPS-induced neutrophil oxygen radical production by TNFα, Infection and Immunity, 4, 1744-1747, 1998). PDE4 inhibitors can very effectively inhibit the release of TNFα from a large number of cells and thus suppress the activity of the neutrophilic granulocytes. The non-specific PDE inhibitor pentoxifylline is able to inhibit both the formation of oxygen radicals and the phagocytosability of neutrophilic granulocytes (Wenisch, C.; Zedtwitz-Liebenstein, K.; Parschalk, B. and Graninger W.: Effect of pentoxifylline in vitro on neutrophil reactive oxygen production and phagocytic ability assessed by flow cytometry, Clin. Drug. Invest., 13(2):99-104, 1997).

Various PDE 4 inhibitors are already known. As a matter of priority, these are xanthine derivatives, rolipram analogues or nitraquazone derivatives (general survey in: Karlsson J-A, Aldos D, Phosphodiesterase 4 inhibitors for the treatment of asthma, Exp. Opin. Ther. Patents 1997, 7: 989-1003). Until now, it was not possible to use any of these compounds clinically. It had to be established that the known PDE 4 inhibitors also have various side-effects such as nausea and emesis, which it was not possible to suppress adequately until now. The discovery of new PDE 4 inhibitors with better therapeutic breadth is therefore necessary.

Although indoles have been playing an important part for many years in the development of new active compounds for various indications, until now hydroxyindoles were completely unknown as inhibitors of PDE 4.

Summary of the Invention

According to a first embodiment of the invention there is provided a hydroxyindole compound of the formula 1



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or a physiologically tolerable salt thereof in which

R^1 is

$-C_{1-12}$-alkyl, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

$-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the

C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4, or

carbo- or heterocyclic saturated or mono- or polyunsaturated spirocycles having 3-10 ring members, where heterocyclic systems contain 1-6 heteroatoms, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4;

R^2 and R^3 are hydrogen or -OH, where at least one of the two substituents must be -OH;

R^4 is -H, -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -COOH, $-(CO)R^6$, $-(CS)R^6$, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_2R^6$;

R^5 is mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members substituted by at least one halogen residue,

optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4, or

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms substituted by at least one halogen atom,

optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$; -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4;

R^6 is -H, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-C_{1-12}$-alkyl, straight-chain or branched-chain, $-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms;

A is either a bond, or $-(CH_2)_m$-, $-(CH_2)_m\text{-}(CH{=}CH)_n\text{-}(CH_2)_p$-, $-(CHOZ)_m$-, -(C=O)-, -(C=S)-, -(C=N-Z)-, -O-, -S-, -NZ-, where m, p = 0-3 and n = 0-2;

Z is -H, or $-C_{1-12}$-alkyl, straight-chain or branched-chain, $-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, or mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms;

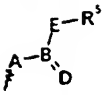
B can either be carbon or sulfur, or -(S=O)-;

D is oxygen, sulfur, CH_2 or N-Z, where D can only be S or CH_2 if B is carbon;

E is a bond, or $-(CH_2)_m$-, -O-, -S-, -(N-Z)-, where m and Z have the meaning defined above.

According to a second embodiment of the invention there is provided a process for the preparation of a compound of formula 1 according to the first embodiment of the invention, characterised in that a compound according to formula 1, for which R^2 or R^3 or R^2 and R^3 = $-O\text{-}R^7$, is converted into a compound of formula 1 according to the first embodiment of the invention by removal of R^7, where R^7 is a substituent suitable as a leaving group.

According to a third embodiment of the invention there is provided a process for the preparation of a compound of formula 1 according to the first embodiment of the invention, characterised in that a compound of the general formula 1 is converted by means of conversions of the sub-structure:



into another compound of the formula 1 according to the first embodiment of the invention.

Also provided by the present invention is a hydroxyindole compound prepared by the process of the second or third embodiment of the invention.

According to a fourth embodiment of the invention there is provided a pharmaceutical composition comprising one or more compounds according to the first embodiment of the invention together with a physiologically tolerable carrier and/or diluent or auxiliary.

According to a fifth embodiment of the invention there is provided a process for the production of a pharmaceutical composition according to the fourth embodiment of the invention which is a medicament, the process being characterised in that one or more compounds according to the first embodiment of the invention are processed to give a pharmaceutical preparation or brought into a therapeutically administrable form using a pharmaceutical carrier and/or diluent or other auxiliary.

According to a sixth embodiment of the invention there is provided the use of a compound as shown in formula 1 according to the first embodiment of the invention as a therapeutically active compound in the manufacture of a medicament for the treatment of a disorder in which the inhibition of TNFα is therapeutically beneficial.

According to a seventh embodiment of the invention there is provided the use of a compound as shown in formula 1 according to the first embodiment of the invention as a therapeutically active compound in the manufacture of a medicament for the treatment of a disorder in which the inhibition of phosphodiesterase 4 is therapeutically beneficial.

According to an eighth embodiment of the invention there is provided the use of a compound as shown in formula 1 according to the first embodiment of the invention as a therapeutically active compound in the manufacture of a medicament for the treatment of a disorder which is connected with the action of eosinophils.

According to a ninth embodiment of the invention there is provided the use of a compound as shown in formula 1 according to the first embodiment of the invention as a therapeutically active compound in the manufacture of a medicament for the treatment of a chronic obstructive pulmonary disease (COPD).

According to a tenth embodiment of the invention there is provided a method for the treatment of a disorder in which the inhibition of TNFα is therapeutically beneficial, which method comprises administering to an animal a therapeutically effective amount of a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention.

According to an eleventh embodiment of the invention there is provided a method for the treatment of a disorder in which the inhibition of phosphodiesterase is therapeutically beneficial, which method comprises administering to an animal a therapeutically effective amount of a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention.

According to a twelfth embodiment of the invention there is provided a method for the treatment of a disorder which is connected with the action of eosinophils, which method comprises administering to an animal a therapeutically effective amount of a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention.

According to a thirteenth embodiment of the invention there is provided a method for the treatment of a chronic obstructive pulmonary disease (COPD), which method comprises administering to an animal a therapeutically effective amount of a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention.

According to a fourteenth embodiment of the invention there is provided a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention when used for the treatment of a disorder in which the inhibition of TNFα is therapeutically beneficial.

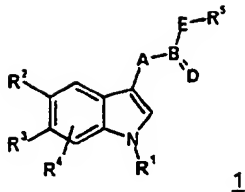
According to a fifteenth embodiment of the invention there is provided a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention when used for the treatment of a disorder in which the inhibition of phosphodiesterase 4 is therapeutically beneficial.

According to a sixteenth embodiment of the invention there is provided a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention when used for the treatment of a disorder which is connected with the action of eosinophils.

According to seventeenth embodiment of the invention there is provided a compound according to the first embodiment of the invention or a pharmaceutical composition according to the fourth embodiment of the invention when used for the treatment of a chronic obstructive pulmonary disease (COPD).

Description of the Invention

The invention relates to substituted hydroxyindoles of the general formula 1



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or a physiologically tolerable salt thereof in which

R^1 is

$-C_{1-12}$-alkyl, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

$-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-O(CO)R^6$, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4, or

carbo- or heterocyclic saturated or mono- or polyunsaturated spirocycles having 3-10 ring members, where heterocyclic systems contain 1-6 heteroatoms, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-O(CO)R^6$, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4;

R^2 and R^3 are hydrogen or -OH, where at least one of the two substituents must be -OH;

R^4 is -H, -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -COOH, $-(CO)R^6$, $-(CS)R^6$, -F, -Cl, -Br, -I, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-O(CO)R^6$, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-SOR^6$, $-SO_2R^6$;

R^5 is mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members substituted by at least one halogen residue,

optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-O(CO)R^6$, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4, or

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms substituted by at least one halogen atom,

optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^5$, $-NO_2$, -CN, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-O(CO)R^6$, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^5$, -COOH, $-(CO)R^5$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4;

R^6 is -H, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-C_{1-12}$-alkyl, straight-chain or branched-chain, $-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms;

A is either a bond, or

$-CH_2)_m-$, $-(CH_2)_m-(CH=CH)_n-(CH_2)_p-$, $-(CHOZ)_m-$, -(C=O)-, -(C=S)-, -(C=N-Z)-, -O-, -S-, -NZ-,

where m, p = 0-3 and n = 0-2 and

Z is

-H, or

$-C_{1-12}$-alkyl, straight-chain or branched-chain,

$-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, which are preferably N, O and S;

B is either carbon or sulfur, or -(S=O)-;

D is oxygen, sulfur, CH_2 or N-Z,

where D can only be S or CH_2 if B is carbon;

E is a bond, or else

$-(CH_2)_m-$, -O-, -S-, -(N-Z)-, where m and Z have the meaning already described beforehand.

The invention furthermore relates to the physiologically tolerable salts of the compounds according to formula 1.

The physiologically tolerable salts are obtained in a customary manner by neutralisation of the bases with inorganic or organic acids or by neutralisation of the acids with inorganic or organic bases. Possible inorganic acids are, for example, hydrochloric acid, sulfuric acid, phosphoric acid or hydrobromic acid, organic acids are, for example, carboxylic, sulfo or sulfonic acids such as acetic acid, tartaric acid, lactic acid, propionic acid, glycolic acid, malonic acid, maleic acid, fumaric acid, tannic acid, succinic acid, alginic acid, benzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, cinnamic acid, mandelic acid, citric acid, malic acid, salicylic acid, 3-aminosalicylic acid, ascorbic acid, embonic acid, nicotinic acid, isonicotinic acid, oxalic acid, amino acids, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid or naphthalene-2-sulfonic acid. Possible inorganic bases are, for example, sodium hydroxide solution, potassium hydroxide solution, ammonia, and possible organic bases are amines, but preferably tertiary amines, such as trimethylamine, triethylamine, pyridine, N,N-dimethylaniline, quinoline, isoquinoline, α-picoline, β-picoline, γ-picoline, quinaldine or pyrimidine.

In addition, physiologically tolerable salts of the compound according to formula 1 can be obtained by converting derivatives which have tertiary amino groups into the corresponding quaternary ammonium salts in a manner known per se using quaternising agents. Possible quaternising agents are, for example, alkyl halides such as methyl iodide, ethyl bromide and n-propyl chloride, but also arylalkyl halides such as benzyl chloride or 2-phenylethyl bromide.

Furthermore, the invention of the compounds of the formula 1 which contain an asymmetric carbon atom relates to the D form, the L form and D,L mixtures and, in the case of a number of asymmetric carbon atoms, the diastereomeric forms. Those compounds of the formula 1 which contain asymmetric carbon atoms and as a rule are obtained as racemates can be separated into the optically active isomers in a manner known per se, for example using an optically active acid. However, it is also possible to employ an optically active starting substance from the start, a corresponding optically active or diastereomeric compound then being obtained as the final product.

Pharmacologically important properties have been found for the compounds according to the invention, which can be utilised therapeutically.

The compounds according to the invention are inhibitors of the release of TNFα.

It is therefore a subject of this invention that the compounds according to formula 1 and their salts, and pharmaceutical preparations which contain these compounds or their salts, can be used for the treatment of disorders in which inhibition of TNFα is beneficial.

These disorders include, for example, arthritides including arthritis and rheumatoid arthritis and other arthritic disorders such as rheumatoid spondylitis and osteoarthritis. Further application possibilities are the treatment of patients who are suffering from sepsis, septic shock, gram-negative sepsis, toxic shock syndrome, respiratory distress syndrome, asthma or other chronic pulmonary disorders, bone resorption diseases or transplant rejection reactions or other autoimmune disorders, such as lupus erythematosus, multiple sclerosis, glomerulonephritis and uveitis, insulin-dependent diabetes mellitus and chronic demyelinisation.

Moreover, the compounds according to the invention can also be employed for the therapy of infections such as virus infections and parasitc infections, for example for the therapy of malaria, infection-related fever, infection-related myalgia, AIDS and cachexia.

The compounds according to the invention are inhibitors of phosphodiesterase 4.

It is therefore a subject of this invention that the compounds according to formula 1 and their salts, and pharmaceutical preparations which contain these compounds or their salts, can be used for the treatment of disorders in which inhibition of phosphodiesterase 4 is beneficial.

Thus the compounds according to the invention can be employed as bronchodilators and for asthma prophylaxis. Compounds according to formula 1 are furthermore inhibitors of the accumulation of eosinophils and their activity. Accordingly, the compounds according to the invention can also be employed in disorders in which eosinophils play a part. These disorders include, for example, inflammatory airway disorders such as bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, eczema, allergic angiitis, inflammations mediated by eosinophils such as eosinophilic fasciitis, eosinophilic pneumonia and PIE syndrome (pulmonary infiltration with eosinophilia), urticaria, ulcerative colitis, Crohn's disease and proliferative skin disorders such as psoriasis or keratosis.

It is a subject of this invention that the compounds according to formula I and their salts can inhibit both the lipopolysaccharide (LPS)-induced release of TNFα in human blood *in vitro*, and the LPS-induced pulmonary neutrophilic infiltration in ferrets and domestic pigs *in vivo*. All the pharmacologically important properties found confirm that the compounds according to formula I and their salts as well as pharmaceutical preparations which contain these compounds or their salts can be used therapeutically for the treatment of chronic obstructive pulmonary diseases.

The compounds according to the invention furthermore have neuroprotective properties and can be used for the therapy of diseases in which neuroprotection is beneficial. Such disorders are, for example, senile dementia (Alzheimer's disease), loss of memory, Parkinson's disease, depression, stroke and intermittent claudication.

Further application possibilities of the compounds according to the invention are the prophylaxis and therapy of prostate diseases, such as, for example, benign prostate hyperplasia, pollakiuria, nocturia, and for the treatment of atony of the bladder and of colics caused by kidney stones.

Finally, the compounds according to the invention can also be used for the inhibition of the development of drug dependence on repeated use of analgesics, such as, for example, morphine, and for the reduction of the development of tolerance on repeated use of these analgesics.

For the production of the medicaments, in addition to the customary auxiliaries, carriers and additives, an efficacious dose of the compounds according to the invention or their salts is used.

The dose of the active compounds can vary depending on the route of administration, age and weight of the patient, nature and severity of the disorders to be treated and similar factors.

The daily dose can be given as an individual dose to be administered once or subdivided into 2 or more daily doses and is, as a rule, 0.001-100mg.

Possible administration forms are oral, parenteral, intravenous, transdermal, topical, inhalational and intranasal preparations.

For administration, possible customary pharmaceutical preparation forms are those such as tablets, coated tablets, capsules, dispersible powders, granules, aqueous solutions, aqueous or oily suspensions, syrup, juices or drops.

Solid pharmaceutical forms can contain inert ingredients and carriers, such as, for example, calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginates, gelatine, guar gum, magnesium or aluminium stearates, methylcellulose, talc, highly disperse salicylic acids, silicone oil, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar or vegetable or animal fats and oils, solid high molecular weight polymers (such as polyethylene glycol); preparations suitable for oral administration can, if desired, contain additional flavourings and/or sweeteners.

Liquid pharmaceutical forms can be sterilised and/or optionally contain auxiliaries such as preservatives, stabilisers, wetting agents, penetrating agents, emulsifiers, spreading agents, solubilisers, salts, sugars or sugar alcohols for regulation of the osmotic pressure or for buffering, and/or viscosity regulators.

Additives of this type are, for example, tartrate and citrate buffers, ethanol, complexing agents (such as ethylenediaminetetraacetic acid and its non-toxic salts). For regulation of the viscosity, possible high molecular weight polymers are those such as, for example, liquid polyethylene oxide, microcrystalline celluloses, carboxymethylcelluloses, polyvinylpyrrolidones, dextrans or gelatine. Solid carriers are, for example, starch, lactose, mannitol, methylcellulose, talc, highly disperse salicylic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular weight polymers such as polyethylene glycol.

Oily suspensions for parenteral or topical application can be vegetable synthetic or semi-synthetic oils such as, for example, liquid fatty acid esters in each case having 8 to 22 C atoms in the fatty acid chains, for example palmitic, lauric, tridecylic, margaric, stearic, arachidic, myristic, behenic, pentadecanoic, linoleic, elaidic, brassidic, erucic or oleic acid, which are esterified with mono- to trihydric alcohols having 1 to 6 C atoms, such as, for example, methanol, ethanol, propanol, butanol, pentanol or their isomers, glycol or glycerol. Fatty acid esters of this type are, for example, commercially available Miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG 6-capric acid, caprylic/capric acid esters of saturated fatty alcohols, polyoxyethylene glycerol trioleates, ethyl oleate, waxy fatty acid esters such as artificial duck preen gland fat, isopropyl cocoate, oleyl oleate, decyl oleate, ethyl lactate, dibutyl phthalate, diisopropyl adipate, polyol fatty acid esters and others. Also suitable are silicone oils of differing viscosities or fatty alcohols such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol or oleyl alcohol, fatty acids such as, for example, oleic acid. Furthermore, vegetable oils such as castor oil, almond oil, olive oil, sesame oil, cottonseed oil, groundnut oil or soya bean oil can be used.

Possible solvents, gel-forming agents and solubilisers are water or water-miscible solvents. Those suitable are, for example, alcohols such as, for example, ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethylene glycols, phthalates, adipates, propylene glycol, glycerol, di- or tripropylene glycol, waxes, methylcellosolve, cellosolve, esters, morpholines, dioxane, dimethylsulfoxide, dimethylformamide, tetrahydrofuran, cyclohexanone etc.

Film-forming agents which can be used are cellulose ethers which can dissolve or swell both in water and in organic solvents, such as, for example, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose or soluble starches.

Mixed forms between gel- and film-forming agents are also perfectly possible. Those used here are especially ionic macromolecules, such as, for example, sodium carboxymethylcellulose, polyacrylic acid, polymethacrylic acid and its salts, sodium

amylopectin semiglycolate, alginic acid or propylene glycol alginate as the sodium salt, gum arabic, xanthan gum, guar gum or carrageenan.

Further formulation auxiliaries which can be employed are: glycerol, paraffin of differing viscosities, triethanolamine, collagen, allantoin, novantisolic acid.

The use of surfactants, emulsifiers or wetting agents can also be necessary for formulation, such as, for example, of Na lauryl sulfate, fatty alcohol ether sulfates, di-Na N-lauryl-β-iminodipropionate, polyethoxylated castor oil or sorbitan monooleate, sorbitan monostearate, polysorbates (eg. Tween), cetyl alcohol, lecithin, glycerol monostearate, polyoxyethylene stearate, alkylphenyl polyglycol ethers, cetyltrimethylammonium chloride or mono-/dialkyl polyglycol ether orthophosphoric acid monoethanolamine salts.

Stabilisers such as montmorillonites or colloidal salicylic acids for the stabilisation of emulsions or for the prevention of the breakdown of the active substances, such as antioxidants, for example tocopherols or butylhydroxyanisole, or preservatives, such as p-hydroxybenzoic acid esters, can likewise optionally be necessary for the preparation of the desired formulations.

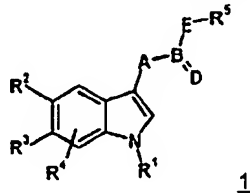
Preparations for parenteral administration can be present in separate dose unit forms such as, for example, ampoules or vials. Preferably, solutions of the active compound are used, preferably aqueous solutions and especially isotonic solutions, but also suspensions. These injection forms can be made available as finished preparations or only prepared directly before administration by mixing the active compound, for example the lyophilisate, if appropriate with further solid carriers, with the desired solvent or suspending agent.

Intranasal preparations can be present as aqueous or oily solutions or as aqueous or oily suspensions. They can also be present as lyophilisates, which are prepared before administration using the suitable solvent or suspending agent.

The production, dispensation and sealing of the preparations is carried out under the customary antimicrobial and aseptic conditions.

The invention furthermore relates to processes for the preparation of the compounds according to the invention.

According to the invention, the compounds of the general formula 1



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having the meanings of R^1, R^2, R^3, R^4, R^5, A, B, D and E shown beforehand are prepared by converting compounds according to formula 1, for which R^2 or R^3 or R^2 and R^3 = -O-R^7, into the compounds according to the invention by removal of R^7.

R^7 in this case represents substituents suitable as leaving groups, such as, for example, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl, acyl, alkoxycarbonyl, aryloxycarbonyl,

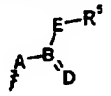
aminocarbonyl, N-substituted aminocarbonyl, silyl or sulfonyl groups, and complexing agents, such as, for example, compounds of boric acid, phosphoric acid and covalently or coordinatively bonded metals, such as zinc, aluminium or copper.

Particularly preferred reactions for the removal of R^7 within the meaning of the preparation process according to the invention are hydrolyses using suitable bases, such as, for example, sodium hydroxide solution, potassium hydroxide solution or sodium carbonate or potassium carbonate.

These hydrolyses are preferably used for R^7 = acyl, alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, N-substituted aminocarbonyl, silyl or sulfonyl groups and complexing agents, such as, for example, compounds of boric acid, phosphoric acid and coordinatively bonded metals, such as zinc, aluminium or copper.

Particularly preferred reactions within the meaning of the preparation process according to the invention for the removal of R^7 from the compounds in which R^7 is an alkyl, cycloalkyl, arylalkyl, aryl or heteroaryl group are ether cleavages, for example by means of hydrobromic acid, hydrochloric acid, hydriodic acid, and using activating Lewis acids, such as, for example, $AlCl_3$, BF_3, BBr_3 or LiCl, in each case in the absence or in the presence of additional activators, such as, for example, ethane-1,2-dithiol or benzyl mercaptan and ether cleavages by means of hydrogen, at elevated pressure or at normal pressure, in the presence of a suitable catalyst, such as, for example, palladium or iridium catalysts.

According to the invention, the compounds of the general formula 1 having the meanings of R^1, R^2, R^3, R^4, R^5, A, B, D and E shown beforehand are also prepared by converting, by means of conversions of the substructure:



by reactions known per se, compounds of the formula 1 according to the invention into other compounds of the formula 1 according to the invention.

Particularly preferred conversion reactions with compounds of the formula 1 according to the invention are, for example, for A = -(C=O)-, reductions to give A = -(CH-OH)- or A = $-CH_2-$ by means of reducing agents known per se, such as, for example, sodium borohydride, or by hydrogenations, which can optionally also be carried out stereoselectively.

Further preferred conversion reactions are the conversion of compounds for which D and E are oxygen into substances in which only D is oxygen, but E is -(N-Z)-, where Z has the meaning already explained.

Working examples

Exemplary preparation processes for compounds of the formula 1 according to the invention from starting substances of the type described, in which R^7 is an alkyl, cycloalkyl, arylalkyl, aryl or heteroaryl group:

Example 1:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide (1)

1.4g of N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-methoxyindol-3-yl]-2-oxoacetamide (3mmol) are dissolved in 100mL of dichloromethane. The solution is heated to reflux and treated with a solution of 14mmol of BBr_3 in 15mL of dichloromethane with stirring. The reaction mixture is refluxed for 3 hours. After cooling, the solution is intensively stirred for 3 hours at 20°C with 200mL of an aqueous sodium hydrogencarbonate solution. The product crystallises out in the course of this. It is isolated, dried at 60°C and recrystallised from 80mL of ethanol.

Yield: 1.1g (80% of theory)

Melting point: 213-214°C

Example 2:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide (1)

5g (38mmol) of anhydrous aluminium chloride are introduced into 50mL of ethane-1,2,-dithiol. A solution of 4.7g of N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-methoxyindol-3-yl]-2-oxoacetamide (10mmol) in 50mL of dichloromethane is added at 0°C. The mixture is stirred at 0°C for 4 hours. 50mL of 10% strength hydrochloric acid are added dropwise at 0-10°C with stirring. The crystallising product is isolated, washed with water and dried at 20°C. A pure product is obtained by recrystallisation from ethanol (180mL).

Yield: 3.1g (67% of theory)

Melting point: 212-214°C

Exemplary preparation process for compounds of the formula 1 according to the invention from starting substances of the type described, in which R^7 is an acyl, alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, N-substituted aminocarbonyl, silyl or sulfonyl group:

Example 3:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide Na salt (2)

5g of N-(3,5-dichloropyridin-4-yl)-2-[5-acetoxy-1-(4-fluorobenzyl)-indol-3-yl]-2-oxoacetamide (10mmol) are stirred at 40-50°C for 1 hour in 50mL of dilute sodium hydroxide solution. The solution is neutralised with hydrochloric acid (10% strength) while cooling with ice and concentrated to dryness. The residue is dissolved in 80mL of acetone. Insoluble constituents are removed. The clear solution is treated with a solution of 0.4g of NaOH in 3mL of water and stirred at 20°C for 2 hours. The crystallised product is isolated, washed with acetone and dried at 60°C.

Yield: 2.44g (51% of theory)

Melting point: 265°C

Exemplary preparation process for compounds of the formula 1 according to the invention from other compounds of the formula 1 according to the invention:

Example 4:

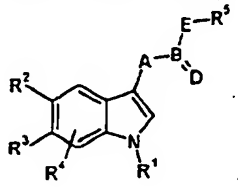
N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-hydroxyacetamide (3)

1g of N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide (1; 2mmol) are suspended in 75mL of methanol. After addition of a solution of 0.2g of sodium borohydride in 3mL of dilute sodium hydroxide solution, the reaction mixture is stirred at 20°C for 6 hours. After the solvent has been removed by distillation, the residue is recrystallised from 40mL of ethanol.

Yield: 0.5g (50% of theory)

Melting point: 205-207°C

Using the exemplary variants indicated, numerous further compounds of the formula 1 can be prepared, of which the following are given by way of example:



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Cpd.	R^1	R^2	R^3	R^4	R^5	A	B	D	E	Melting point [°C]
1	4-Fluorobenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	215
2	4-Fluorobenzyl	$-O^- Na^+$	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	265
3	4-Fluorobenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(CHOH)-	C	O	-(N-H)-	205-207
4	2,6-Difluorobenzyl	-OH	-H	-H	4-Pyridyl	-(C=O)-	C	O	-(N-H)-	327-329
5	2,6-Difluorobenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	266-268
6	3-Nitrobenzyl	$-O^- Na^+$	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	235-238 dec.
7	n-Propyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	280-282
8	Isopropyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	245-247
9	Cyclopentylmethyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	246-248
10	4-Fluorobenzyl	-OH	-H	-H	2,6-Dichlorophenyl	-(C=O)-	C	O	-(N-H)-	216-218
11	4-Fluorobenzyl	-OH	-H	-H	2,6-Dichloro-4-trifluoromethylphenyl	-(C=O)-	C	O	-(N-H)-	199-201
12	4-Fluorobenzyl	-OH	-H	-H	2,6-Dichloro-4-trifluoromethoxyphenyl	-(C=O)-	C	O	-(N-H)-	176-178
13	4-Fluorobenzyl	-H	-OH	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	212-213
14	4-Methoxybenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-	C	O	-(N-H)-	239-241

The compounds according to the invention are strong inhibitors of phosphodiesterase 4 and TNFα release. Their therapeutic potential is confirmed *in vivo*, for example, by the inhibition of the asthmatic late-phase reaction (eosinophilia) in guinea-pigs and by the influencing of the allergen-induced vascular permeability in actively-sensitised brown Norway rats.

Inhibition of phosphodiesterase

The PDE 4 activity is determined in enzyme preparations of human polymorphonuclear lymphocytes (PMNLs), the PDE 2, 3 and 5 activity with PDE from human platelets. Human blood was anticoagulated with citrate. The thrombocyte-rich plasma in the supernatant is separated from the erythrocytes and leucocytes by centrifugation at 700 ×g for 20 minutes at RT. The platelets are lysed by ultrasound and employed in the PDE 3 and PDE 5 assay. For the determination of the PDE 2 activity, the cytosolic platelet fraction is purified on an anion exchange column by means of NaCl gradients and the PDE 2 peak is recovered for the assay. The PMNLs for the PDE 4 determination are isolated by a following dextran sedimentation and subsequent gradient centrifugation using Ficoll-Paque. After a second washing of the cells, the erythrocytes still contained are lysed in the course of 6 minutes at 4°C by the addition of 10mL of hypotonic buffer (155mM NH_4Cl, 10mM $NaHCO_3$, 0.1mM EDTA, pH7.4). The still intact PMNLs are washed with PBS a further two times and lysed by means of ultrasound. The supernatant of a one-hour centrifugation at 4°C at 48 000 ×g contains the cytosolic fraction of the PDE 4 and is employed for the PDE 4 measurements.

The phosphodiesterase activity is determined with some modifications according to the method described by Thompson et al. (Thompson, W.J.; Appleman, M.M., Assay of cyclic nucleotide phosphodiesterase and resolution of multiple molecular forms of the enzyme, Adv. Cycl. Nucl. Res. 1979, 10, 69-92).

The reaction mixtures contain 50mM tris HCl (pH7.4), 5mM$MgCl_2$, the inhibitors in variable concentrations, the corresponding enzyme preparation and also the further components necessary for the detection of the individual isoenzymes (see below). The reaction is started by the addition of the substrate 0.5μM [^{3}H]-cAMP or [^{3}H]-cGMP (about 6000 CPM/test). The final volume is 100mL. Test substances are prepared as stock solutions in DMSO. The DMSO concentration in the reaction mixture is 1% v/v. At this DMSO concentration, the PDE activity is not affected. After the start of the reaction by means of substrate addition, the samples are incubated at 37°C for 30 minutes. The reaction is stopped by heating the test tubes for 2 minutes at 110°C. The samples remain in the ice for a further 10 minutes. After the addition of 30μL of 5'-nucleotidase (1mg/mL, of a snake venom suspension from *Crotalus adamanteus*) incubation is carried out for 10 minutes at 37°C. The samples are stopped on ice, 400μL each of a mixture of Dowex-water-ethanol (1+1+1) are added, and the samples are well mixed and again incubated on ice for 15 minutes. The reaction vessels are centrifuged at 3000 ×g for 20 minutes. 200μL aliquots of the

supernatant are transferred directly to scintillation vessels. After the addition of 3mL of scintillator, the samples are measured in a beta counter.

[^{3}H]-cAMP is used as a substrate for the determination of the PDE 4, 3 and 2 activity, [^{3}H]-cGMP for the determination of the PDE 5 activity. The non-specific enzyme activities in each case are determined in the presence of 100μM rolipram in the case of PDE 4 and in the presence of 100μM IBMX in the determination of PDE 3 and 5 and subtracted from the test values. The incubation batches of the PDE 3 assay contain 10μM rolipram in order to inhibit possible contamination by the PDE 4. The PDE 2 is tested using an SPA assay from Amersham. The assay is carried out in the presence of the activator of PDE 2 (5μM cGMP).

IC_{50} values in the range from 10^{-9} to 10^{-5} M were calculated for the compounds according to the invention in relation to the inhibition of phosphodiesterase 4. The selectivity to the PDE types 2, 3 and 5 is factor 100 to 10,000.

Inhibition of TNFα release from cells of nasal polyps

The experimental arrangement essentially corresponds to the method described by Campbell, A.M. and Bousquet J (Anti-allergic activity of H_1-blockers, Int. Arch. Allergy Immunol., 1993, 101, 308-310). The starting material is nasal polyps (operation material) of patients who have been subjected to surgical treatment.

The tissue is washed with RPMI 1640 and then broken down at 37°C for 2 h using protease (2.0mg/mL), collagenase (1.5mg/mL), hyaluronidase (0.75mg/mL) and DNAse (0.05mg/mL) (1g of tissue to 4mL of RPMI 1640 with enzymes). The cells obtained, a mixture of epithelial cells, monocytes, macrophages, lymphocytes, fibroblasts and granulocytes, are filtered and washed by repeated centrifugation in nutrient solution, passively sensitised by addition of human IgE and the cell suspension is adjusted to a concentration of 2 million cells/mL in RPMI 1640 (supplemented with antibiotics, 10% foetal calf serum, 2mM glutamine and 25mM Hepes). This suspension is distributed in 6-well cell culture plates (1mL/well). The cells are preincubated for 30 min with the test substances in various final concentrations and then stimulated to TNFα release by addition of anti-IgE (7.2μg/mL). The maximum release into the nutrient medium takes place after about 18 hours. In this period, the cells are incubated at 37°C and 5% CO_2. The nutrient medium (supernatant) is recovered by centrifugation (5 min, 4000rpm) and stored at -70°C until cytokine determination. The determination of TNFα in the supernatant is carried out using so-called sandwich ELISAs (basic material Pharmingen), in which concentrations of the cytokine in the range from 30-1000pg/mL can be detected.

Cells not stimulated with anti-IgE barely produce TNFα, stimulated cells, however, secrete large amounts of TNFα, which can be decreased in a dose-dependant manner, for example, by PDE 4 inhibitors. The IC_{50} (concentration at 50% inhibition) is calculated from the percentage inhibition (TNFα release of the cells stimulated with anti-IgE = 100%) of the tested substances at various concentrations.

For the compounds according to the invention, IC_{50} values in the range of 10^{-7} to 10^{-5} M were determined.

Inhibition of the late-phase eosinophilia 24 h after inhalational ovalbumin challenge of actively sensitised guinea-pigs

The inhibition of the pulmonary eosinophil infiltration by the substances is investigated in an *in vivo* test on male Dunkin-Hartley guinea-pigs (200-250g) actively sensitised against ovalbumin (OVA). The sensitisation is carried out by means of two intraperitoneal injections of a suspension of 20µg of OVA together with 20mg of aluminium hydroxide as an adjuvant in 0.5mL of physiological saline solution per animal on two successive days. 14 days after the second injection, the animals are pretreated with mepyramine maleate (10mg/kg i.p.) in order to protect them from anaphylactic death. 30 minutes later, the animals are exposed for 30 sec in a plastic box to an OVA aerosol (0.5mg/mL) which is generated by a nebuliser driven with compressed air (19.6 kPa) (allergen challenge). Control animals are nebulised with physiological saline solution. 24 hours after the challenge, the animals are anaesthetised with an overdose of ethylurethane (1.5g/kg of body weight i.p.) and a bronchoalveolar lavage (BAL) is carried out using 2 × 5mL of physiological saline solution. The BAL fluid is collected, centrifuged at 300rpm for 10 min and the cell pellet is then resuspended in 1mL of physiological saline solution. The eosinophils in the BAL are counted using an automatic cell differentiation apparatus (Bayer Diagnostics Technicon H1). 2 control groups (nebulisation with physiological saline solution and nebulisation with OVA solution) are included in each test.

The percentage inhibition of eosinophilia of the test group treated with substance is calculated according to the following formula:

$$\% \text{ inhibition} = 100 - \frac{100 \cdot (B-C)}{(A-C)}$$

A = Eosinophils in the control group with OVA challenge and vehicle

B = Eosinophils in the group with OVA challenge treated with substance

C = Eosinophils in the control group with 0.9% strength NaCl challenge and vehicle

The test substances are administered intraperitoneally or orally as a suspension in 10% polyethylene glycol 300 and 0.5% strength 5-hydroxyethylcellulose 2 hours before the allergen challenge. The control groups are treated with the vehicle according to the administration form of the test substance.

The compounds according to the invention inhibit late-phase eosinophilia by 30% to 80% after intraperitoneal administration of 10mg/kg and by 40% to 70% after oral administration of 30mg/kg.

The compounds according to the invention are thus particularly suitable for the production of medicaments for the treatment of disorders which are connected with the action of eosinophils.

Effect of allergen-induced vascular permeability on actively sensitised brown Norway rats

Male brown Norway rats weighing 280-300g are actively sensitised on 2 successive days by intraperitoneal injection of a suspension of 1mg of ovalbumin together with 100mg of aluminium hydroxide in 1mL/animal. Three weeks after sensitisation, the rats are

anaesthetised with sodium thiopental and fixed in the supine position. For perfusion of the nasal cavity, a polyethylene catheter was advanced into the trachea in a backwards direction as far as the internal opening of the choanas, so that it was possible for the solution to trickle out through the nasal cavities. A short tracheal catheter was tied into the trachea in an orthograde manner in order to make respiration possible. For perfusion, phosphate-buffered saline solution (PBS) was continuously pumped through the nasal cavity (0.5mL/min) using a roller pump and collected by means of a fraction collector. Evans Blue was used as a plasma marker and injected intravenously (1mL/animal each of a 1% strength solution in PBS) through a catheter in the jugular vein.

Substance administration was carried out topically. During this administration, the test substance was added to the perfusion medium (PBS). The nasal mucous membrane was perfused for 30 min with PDE 4 inhibitor-containing solution. Evans Blue was then injected immediately before the start of the perfusion with ovalbumin-containing solution (challenge). After the start of the ovalbumin challenge (10mg/mL of ovalbumin dissolved in PBS) 15 min fractions were collected every 15 min in the fraction collector over a period of 60 min. The Evans Blue concentration in the perfusates was measured with a Digiscan photometer at a wavelength of 620nm. The blank values were automatically subtracted in the course of this. The course of action over 60 min was calculated using an AUC program. The substance action of the preparation group was calculated against vehicle controls in %.

For the compounds according to the invention, IC_{50} values in the range from 10^{-8} to 10^{-5} M were determined.

The utility of the compounds according to the invention as in formula I for the therapy of chronic obstructive pulmonary diseases is confirmed by the inhibition of LPS-induced TNFα release in human blood and by the inhibition of LPS-induced pulmonary neutrophil infiltration in ferrets and domestic pigs.

The stimulation of isolated leucocytes to cytokine release can take place in various ways. Lipopolysaccharides (LPSs) are a stimulus suitable for the investigation of TNFα release. LPS is a constituent of the bacterial cell walls and is released by killing the bacteria (antibiotics or immune system). LPS particularly stimulates the activity of the phagocytising leucocytes (tissue macrophages, granulocytes, monocytes) and causes the infiltration of leucocytes from the blood stream into the affected tissue. A cytokine important for these mechanisms is TNFα, which is secreted in large amounts by the affected cells (the monocytes and macrophages are the main source) and initiates and maintains inflammation alongside other mediators.

LPS-induced TNFα release in human blood diluted 1:5

For the investigation of the effect on TNFα release, blood was obtained from various donors (inhibition of coagulation by means of citrate) and diluted 1:5 with RPMI 1640 cell culture medium. The test substances were added to the samples in various concentrations before the LPS challenge. The stimulation of the leucocytes was carried out 30 min later using lipopolysaccharides (LPS) *from Salmonella abortus equi* in a final concentration of

10µg/mL. After incubation of the test batches for 24 hours at 37°C and under 5% CO_2 in an incubator, the diluted blood was centrifuged and the TNFα concentration in the cell-free supernatant was measured by means of ELISA.

IC_{50} values in the range from 10^{-7} to 10^{-5}M were determined for the compounds according to the invention. An IC_{50} value of 0.8µmol/L, for example, was determined for the compound as in working example 1. In comparison with this, an IC_{50} value of 7.0µmol/L was determined with the reference standard SB 207499.

Inhibition of lipopolysaccharide (LSP)-induced neutrophilia in ferrets

The inhibition of the pulmonary neutrophil infiltration by the substance is investigated in an *in vivo* test on male ferrets (0.6-2kg). The experimental animals are anaesthetised with pentobarbital sodium (40mg/kg of body weight i.p.), placed individually into a closed nebulisation box of capacity 5 l and exposed to an ultrasonically nebulised aerosol of 0.01% strength LPS (lipopolysaccharide) solution (additionally 0.1% hydroxylamine in PBS) for 10 minutes. The aerosol is generated by a nebuliser driven with compressed air (0.2 Mpa). Control animals are treated with an aerosol of physiological saline solution. The animals are observed during the entire process and removed from the nebulisation box after admission of fresh air. On inhalation, nebulised LPS immediately induces inflammation of the airways, which is characterised by a massive infiltration of neutrophilic granulocytes into the lungs of the experimental animals. The neutrophilia achieves its maximum 4 to 6 hours after LPS exposure. In order to be able to measure the number of infiltrated neutrophilic granulocytes, the animals are anaesthetised with an overdose of ethylurethane (1.5g/kg of body weight i.p.) 6 hours after LPS provocation and a bronchioalveolar [sic] lavage (BAL) is carried out using 2 x.10mL of physiological saline solution. The number of cells in the pooled original BAL fluid (100µL) are determined using the Technicon H1E automatic cell-counting apparatus (Bayer Diagnostic) and the different leucocytes per µL are differentiated. In each test, 2 control groups (nebulisation with physiological saline solution or with LPS solution) are included. Substances having anti-inflammatory activity, particularly those which affect TNFα release or the function of the neutrophilic granulocytes, inhibit the infiltration of leucocytes. The inhibition of infiltration is determined by the comparison of the number of infiltrated neutrophils in untreated experimental animals (with and without LPS provocation).

ID_{50} values in the range from 1 to 20mg/kg i.p. were determined for the compounds according to the invention. The compound as in working example 1 was administered, for example, in the doses 1, 3 and 10mg/kg i.p. 2 hours before LPS provocation to up to 3 experimental animals per dose. The neutrophilia in the BAL was inhibited in a dose-dependent manner (18%, 64% and 78%). The ID_{50} is 2.4mg/kg i.p.

The administration of the selected PDE 4 inhibitor RPR-73401 (reference substance) caused an inhibition of neutrophilia of 49% in the dose 1mg/kg i.p.

For intrapulmonary administration, the trachea of the animals is opened up under anaesthesia (40mg/kg i.p. of pentobarbital sodium, 3% strength, 1.3mL/kg), a 7cm-long

PVC catheter is tied in and the test substances are administered intrapulmonarily in powder form (mixed with lactose to 20mg/kg) by means of a syringe 2 hours before LPS provocation.

The intrapulmonary administration of the compound as in working example 1 in the doses 1, 3 and 10mg/kg inhibits LPS-induced neutrophilia in a dose-dependent manner (43%, 65% and 100%). The ID_{50} is 1.65mg/kg i.palm.

LPS-induced neutrophilia in the domestic pig

Pulmonary neutrophilia can be induced in the domestic pig in a manner similar to that in the ferret. The animals are anaesthetised (pentobarbital 10mg/kg i.v.) and intubated. Using a bronchoscope, a partial bronchoalveolar lavage is carried out in order to determine the proportion of neutrophilic granulocytes under physiological conditions. The test substance is then administered and the animals inhale an ultrasonically nebulised aerosol of 0.03% strength LPS (lipopolysaccharide) solution (additionally 0.1% hydroxylamine in PBS) through the tracheal tube for 20 min. The inhaled LPS induces a reactive inflammation of the airways and neutrophilic granulocytes infiltrate on a huge scale. The neutrophilia achieves its maximum 4 to 6 hours after LPS exposure. After 6 hours, the bronchioalveolar [sic] lavage is repeated and the increase in the neutrophil count is determined arithmetically.

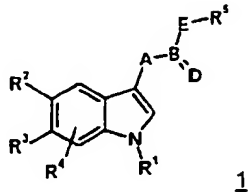
The pig animal species is particularly suitable for these investigations, since there are large anatomical and physiological similarities to man.

For the compounds according to the invention, inhibitions of LPS-induced neutrophilia of 20% to 65% were determined on intrapulmonary administration of 10mg/animal.

The intrapulmonary administration of the compound as in working example 1 in the dose 10mg/animal (about 0.75mg/kg) inhibited LPS-induced pulmonary neutrophilia by 51%.

The claims defining the invention are as follows:

1. A hydroxyindole compound of the formula 1



1

or a physiologically tolerable salt thereof in which

R^1 is

$-C_{1-12}$-alkyl, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

$-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4,

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4, or

carbo- or heterocyclic saturated or mono- or polyunsaturated spirocycles having 3-10 ring members, where heterocyclic systems contain 1-6 heteroatoms, optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4;

R^2 and R^3 are hydrogen or -OH, where at least one of the two substituents must be -OH;

R^4 is -H, -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^5$, $-NO_2$, -CN, -COOH, $-(CO)R^6$, $-(CS)R^6$, -F, -Cl, -Br, -I, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_2R^6$;

R^5 is mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members substituted by at least one halogen residue,

optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, $-O\text{-}C_{1-6}$-alkyl, $-O\text{-}C_{6-14}$-aryl, $-O(CO)R^6$, $-S\text{-}C_{1-6}$-alkyl, $-S\text{-}C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4, or

mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms substituted by at least one halogen atom,

optionally mono- or polysubstituted by -OH, -SH, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-NHCOR^6$, $-NO_2$, -CN, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-O(CO)R^5$, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-SOR^6$, $-SO_3H$, $-SO_2R^6$, $-OSO_2C_{1-6}$alkyl, $-OSO_2C_{6-14}$aryl, $-(CS)R^6$, -COOH, $-(CO)R^6$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms, where the C_{6-14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R^4;

R^6 is -H, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC_{6-14}$aryl, $-N(C_{6-14}\text{aryl})_2$, $-N(C_{1-6}\text{alkyl})(C_{6-14}\text{aryl})$, $-O-C_{1-6}$-alkyl, $-O-C_{6-14}$-aryl, $-S-C_{1-6}$-alkyl, $-S-C_{6-14}$aryl, $-C_{1-12}$-alkyl, straight-chain or branched-chain, $-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms;

A is either a bond, or $-(CH_2)_m$-, $-(CH_2)_m-(CH=CH)_n-(CH_2)_p$-, $-(CHOZ)_m$-, -(C=O)-, -(C=S)-, -(C=N-Z)-, -O-, -S-, -NZ-, where m, p = 0-3 and n = 0-2;

Z is -H, or $-C_{1-12}$-alkyl, straight-chain or branched-chain, $-C_{2-12}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3-14 ring members, or mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5-15 ring members and 1-6 heteroatoms;

B can either be carbon or sulfur, or -(S=O)-;

D is oxygen, sulfur, CH_2 or N-Z, where D can only be S or CH_2 if B is carbon;

E is a bond, or $-(CH_2)_m$-, -O-, -S-, -(N-Z)-, where m and Z have the meaning defined above.

2. A compound as shown in formula 1 according to claim 1, wherein the 1-6 heteroatoms whenever referred to in claim 1 are selected from N, O and S.

3. A physiologically tolerable salt of a compound as shown in formula 1 according to claim 1 or 2, wherein bases have been neutralised with inorganic or organic acids, acids have been neutralised with inorganic or organic bases, or tertiary amines have been quaternised to give quaternary ammonium salts.

4. A compound as shown in formula 1 according to any one of claims 1 to 3 having an asymmetric carbon atom in the D form, the L form and D,L mixtures, and, in the case of a number of asymmetric carbon atoms, the diastereomeric forms.

5. A compound as shown in formula 1 according to any one of claims 1 to 4, wherein the compound is selected from the group consisting of the following compounds:

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide Na salt;

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-hydroxyacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(2,6-difluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(3-nitrobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide Na salt;

N-(3,5-dichloropyridin-4-yl)-2-(1-propyl-5-hydroxyindol-3-yl)-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-(1-isopropyl-5-hydroxyindol-3-yl)-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-(1-cyclopentylmethyl-5-hydroxyindol-3-yl)-2-oxoacetamide;

N-(2,6-dichlorophenyl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-6-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-5-hydroxy-1-(4-methoxybenzyl)indole-3-carboxamide.

6. The compound N-(3,5-dichloropyridine-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindole-3-yl]-2-oxoacetamide and pharmaceutically acceptable salts thereof.

7. An hydroxyindole compound, substantially as hereinbefore described with reference to any one of Examples 1 to 3, 5 to 10, 13 or 14.

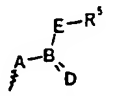
8. A process for the preparation of a compound as shown in formula 1 according to any one of claims 1 to 4, characterised in that a compound according to formula 1, for which R^2 or R^3 or R^2 and R^3 = -O-R^7, is converted into a compound of formula 1 according to any one of claims 1 to 4 by removal of R^7, where R^7 is a substituent suitable as a leaving group.

9. The process according to claim 8, wherein R^7 is selected from alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl, acyl, alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, N-substituted aminocarbonyl, silyl or sulfonyl groups, and complexing agents.

10. The process according to claim 9, wherein the complexing agents are selected from compounds of boric acid, phosphoric acid and covalently or coordinatively bonded metals.

11. The process according to claim 10 wherein the covalently or coordinatively bonded metals are selected from zinc, aluminium and copper.

12. A process for the preparation of a compound as shown in formula 1 according to any one of claims 1 to 4, characterised in that a compound of the general formula 1 is converted by means of conversions of the sub-structure:



into another compound of the formula 1 according to any one of claims 1 to 4.

13. A process for the preparation of a hydroxyindole compound wherein the process is substantially as hereinbefore described with reference to any one of Examples 1 to 3, 5 to 10, 13 or 14.

14. A hydroxyindole compound prepared by the process of any one of claims 8 to 13.

15. A pharmaceutical composition comprising one or more compounds according to any one of claims 1 to 7 or 14 together with a physiologically tolerable carrier and/or diluent or auxiliary.

16. A process for the production of a pharmaceutical composition according to claim 15 which is a medicament, the process being characterised in that one or more compounds according to any one of claims 1 to 7 or 14 are processed to give a pharmaceutical preparation or brought into a therapeutically administrable form using a pharmaceutical carrier and/or diluent or other auxiliary.

17. Use of a compound as shown in formula 1 according to any one of claims 1 to 7 or 14 as a therapeutically active compound in the manufacture of a medicament for the treatment of a disorder in which the inhibition of TNFα is therapeutically beneficial.

18. Use of a compound as shown in formula 1 according to any one of claims 1 to 7 or 14 as a therapeutic active compound in the manufacture of a medicament for the treatment of a disorder in which the inhibition of phosphodiesterase 4 is therapeutically beneficial.

19. Use of a compound as shown in formula 1 according to any one of claims 1 to 7 or 14 as a therapeutically active compound in the manufacture of a medicament for the treatment of a disorder which is connected with the action of eosinophils.

20. Use of a compound as shown in formula 1 according to any one of claims 1 to 7 or 14 as a therapeutically active compound in the manufacture of a medicament for the treatment of a chronic obstructive pulmonary disease (COPD).

21. A method for the treatment of a disorder in which the inhibition of TNFα is therapeutically beneficial, which method comprises administering to an animal a therapeutically effective amount of a compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15.

22. A method for the treatment of a disorder in which the inhibition of phosphodiesterase is therapeutically beneficial, which method comprises administering to an animal a therapeutically effective amount of a compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15.

23. A method for the treatment of a disorder which is connected with the action of eosinophils, which method comprises administering to an animal a therapeutically effective amount of a compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15.

24. A method for the treatment of a chronic obstructive pulmonary disease (COPD), which method comprises administering to an animal a therapeutically effective amount of a compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15.

25. A compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15 when used for the treatment of a disorder in which the inhibition of TNFα is therapeutically beneficial.

26. A compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15 when used for the treatment of a disorder in which the inhibition of phosphodiesterase 4 is therapeutically beneficial.

27. A compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15 when used for the treatment of a disorder which is connected with the action of eosinophils.

28. A compound according to any one of claims 1 to 7 or 14 or a pharmaceutical composition according to claim 15 when used for the treatment of a chronic obstructive pulmonary disease (COPD).

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